CHEST

Hypoxic Pulmonary Vasoconstriction
From Molecular Mechanisms to Medicine

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Hypoxic pulmonary vasoconstriction (HPV) is a homeostatic mechanism that is intrinsic to the pulmonary vasculature. Intrapulmonary arteries constrict in response to alveolar hypoxia, diverting blood to better-oxygenated lung segments, thereby optimizing ventilation/perfusion matching and systemic oxygen delivery. In response to alveolar hypoxia, a mitochondrial sensor dynamically changes reactive oxygen species and redox couples in pulmonary artery smooth muscle cells (PASMC). This inhibits potassium channels, depolarizes PASMC, activates voltage-gated calcium channels, and increases cytosolic calcium, causing vasoconstriction. Sustained hypoxia activates rho kinase, reinforcing vasoconstriction, and hypoxia-inducible factor (HIF)-1α, leading to adverse pulmonary vascular remodeling and pulmonary hypertension (PH). In the nonventilated fetal lung, HPV diverts blood to the systemic vasculature. After birth, HPV commonly occurs as a localized homeostatic response to focal pneumonia or atelectasis, which optimizes systemic P_{O_2} without altering pulmonary artery pressure (PAP). In single-lung anesthesia, HPV reduces blood flow to the nonventilated lung, thereby facilitating thoracic surgery. At altitude, global hypoxia causes diffuse HPV, increases PAP, and initiates PH. Exaggerated or heterogeneous HPV contributes to high-altitude pulmonary edema. Conversely, impaired HPV, whether due to disease (eg, COPD, sepsis) or vasodilator drugs, promotes systemic hypoxemia. Genetic and epigenetic abnormalities of this oxygen-sensing pathway can trigger normoxic activation of HIF-1α and can promote abnormal metabolism and cell proliferation. The resulting pseudohypoxic state underlies the Warburg metabolic shift and contributes to the neoplasia-like phenotype of PH. HPV and oxygen sensing are important in human health and disease. CHEST 2017; 151(1):181-192

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Hypoxic pulmonary vasoconstriction (HPV) was initially identified by Bradford and Dean[1] and subsequently characterized by von Euler and Liljestrand.[2] HPV is the lung's intrinsic mechanism for matching perfusion to ventilation to optimize systemic oxygen

ABBREVIATIONS: ATP = adenosine triphosphate; Ca_L = voltage-gated calcium channels; ETC = electron transport chain; $FADH_2$ = flavin adenine dinucleotide; HAPE = high-altitude pulmonary edema; HIF = hypoxia-inducible factor; HPH = hypoxic pulmonary hypertension; HPV = hypoxic pulmonary vasoconstriction; Kv = voltage-gated potassium channels; mPAP = mean pulmonary artery pressure; NADH = nicotinamide adenine dinucleotide; NO = nitric oxide; PA = pulmonary artery; PAP = pulmonary artery pressure; PASMC = pulmonary artery smooth muscle cell; PH = pulmonary hypertension; ROS = reactive oxygen species; SOD2 = superoxide dismutase 2; $\dot{V}/\dot{Q}$ = ventilation/perfusion

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delivery. HPV reflects the constriction of small intrapulmonary arteries in response to alveolar hypoxia.[3] HPV can be global (in response to environmental hypoxia), in which case pulmonary artery pressure (PAP) rises; however, in most cases HPV is elicited by focal atelectasis or pneumonia, and both the alveolar hypoxia and the vasoconstriction are localized to a lung segment or lobe. In such cases, blood is diverted from the hypoxic lung segment to a better-oxygenated portion of the lung without elevation of PAP. Using the combination of a chest roentgenogram and a radioisotope ventilation/perfusion ($\dot{V}/\dot{Q}$) scan, the matching $\dot{V}/\dot{Q}$ defect due to parenchymal lung disease and HPV (Fig 1A) is readily distinguished from the mismatched $\dot{V}/\dot{Q}$ defect caused by pulmonary embolism (Fig 1B).

HPV has its onset within seconds of exposure to hypoxia and reaches a maximum intensity within minutes.[4,5] Although HPV can be sustained, it remains reversible on restoration of normal airway oxygen levels, unless pulmonary hypertension (PH) and adverse vascular remodeling has occurred. The reversibility of sustained lobar HPV is illustrated by a patient whose endobronchial adenoma caused longstanding left lung atelectasis and a matching $\dot{V}/\dot{Q}$ abnormality, both of which reversed after resection of the adenoma.[6] The vasoconstrictor response to hypoxia is unique to the resistance PAs[7]; the systemic vasculature (eg, renal, mesenteric, and cerebral arteries) dilates in response to hypoxia (which also serves to increase tissue oxygen delivery[8-10]).

Mechanism of HPV

The sensor and effector mechanisms of HPV have been the subject of considerable research.[11-15] The sensor mechanism of HPV is hypothesized to reside within the mitochondria.[16] The classically recognized function of the mitochondria is the generation of energy (adenosine triphosphate [ATP]). Electron transport from the electron donors, nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) occurs along the electron transport chain (ETC). Electron flux between ETC components is mediated by lipid-soluble semiquinones within the cristae. As electrons flow down a redox gradient to the terminal electron receptor (molecular oxygen), protons are transported across the inner mitochondrial membrane. According to Mitchell's chemiosmotic theory,[17] the buildup of hydrogen ions across this membrane generates the electrochemical gradient that powers an H^+ transporter, the F_1F_O adenosine triphosphatase complex, and promotes ATP synthesis.[18]

Mitochondria are prokaryotic endosymbionts that evolved within eukaryotic cells to support the energy demands of multicellular organisms.[19] It is increasingly recognized that they have many noncanonical functions including oxygen sensing.[20] Mitochondria form dynamic networks shaped by fission, fusion, and translocation. Live-cell imaging of the mitochondrial network suggests an analogy to the electrical wiring in a building (Fig 2, Video 1). Unlike the static two-dimensional electron microscopic images in fixed-tissue preparations, which make these organelles appear isolated, the use of mitochondria-targeted fluorophores in living pulmonary artery smooth muscle cells (PASMC) reveals that mitochondria form a pervasive and dynamic reticulum that reaches all areas of the cell and dynamically contacts other organelles, such as the sarcoplasmic reticulum. An appreciation of mitochondrial form aids understanding of the sensor function.

The sensor function of mitochondria is a byproduct of physiological electron flux, as illustrated in Figure 3. Briefly, during electron transfer some uncoupled electrons generate reactive oxygen species (ROS), specifically superoxide, which is rapidly converted by superoxide dismutase 2 (SOD2) to hydrogen peroxide, a diffusible redox mediator, which modulates the activity of redox-sensitive ion channels and enzymes and serves as a signaling molecule.[21,22] Teleologically, an oxygen sensor that relies on a parameter linked to P_{O_2}, (namely, ROS production that occurs as a byproduct of electron flux) but that resides proximal to ATP synthesis, permits a homeostatic response to counter hypoxia, without risking bioenergetic compromise. Oxygen sensing within the mammalian homeostatic oxygen sensing system relies on redox chemistry controlled by mitochondria and other redox sensors.[23]

Although increased by endothelium-derived vasoconstrictors (eg, endothelin and thromboxane) and inhibited by endothelium-derived vasodilators (eg, nitric oxide and prostacyclin), the core effector mechanism of HPV lies within the PASMC. Here HPV is triggered by a mitochondrial redox signal that involves the coordinated response of voltage- and redox-sensitive potassium and calcium channels (Fig 3). Briefly, voltage-gated potassium channels (Kv) maintain a resting membrane potential of about –60 mV (reflective of tonic egress of K^+ from the PASMC). This negative membrane potential decreases the opening of voltage-gated, L-type calcium channels. Outward potassium current is inhibited during hypoxia, depolarizing the membrane and increasing the open-state probability of calcium

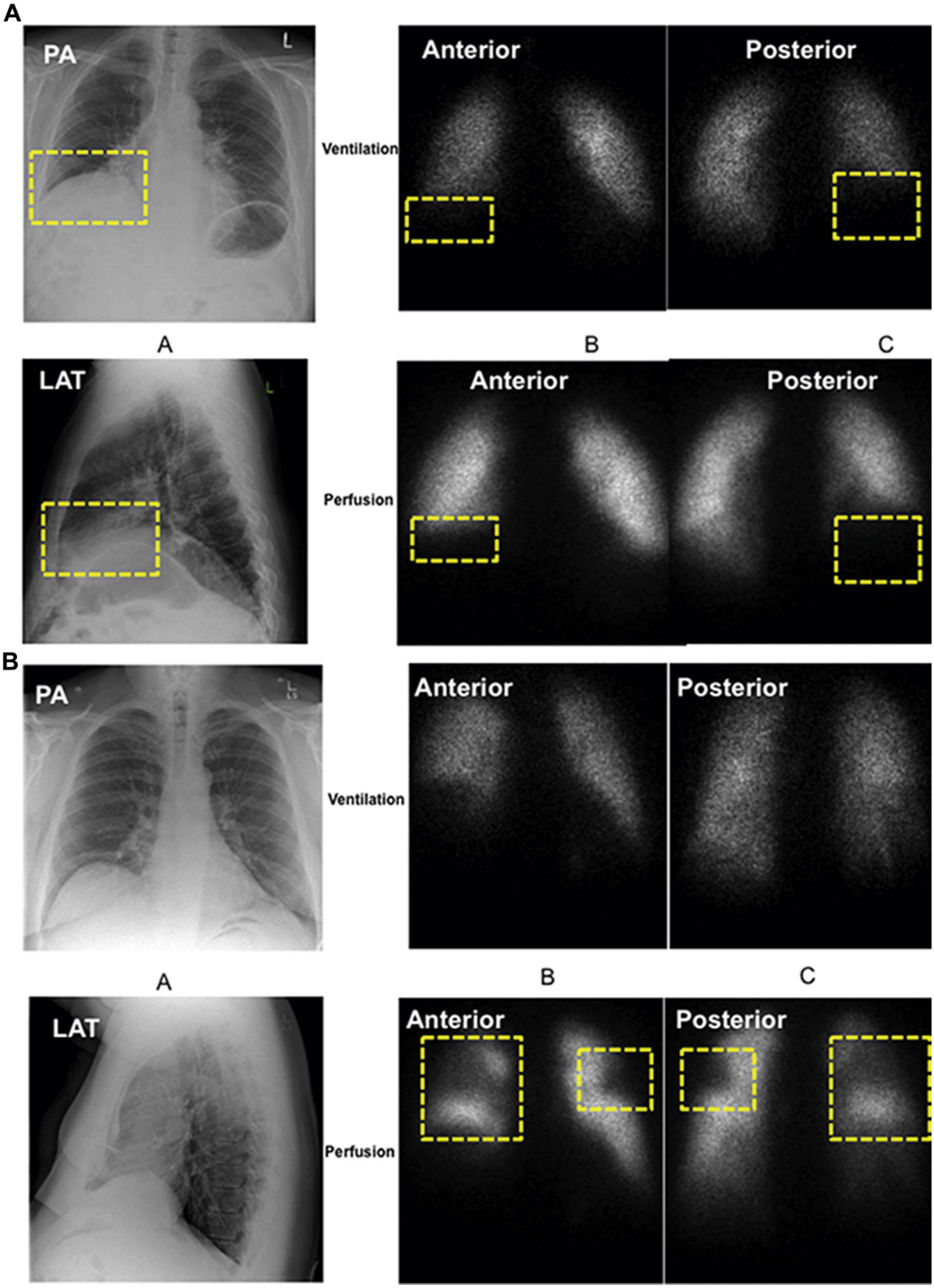


Figure 1 – *Matched vs mismatched ventilation/perfusion ($\dot{V}/\dot{Q}$) defects. (A) Matched $\dot{V}/\dot{Q}$ defect due to interstitial lung disease. An 83-year-old man with shortness of breath on exertion. Chest CT showed interstitial lung disease with a basal predominance consistent with usual interstitial pneumonitis. (B) Mismatched defect indicating pulmonary embolism. A 57-year-old man with obesity, hypertension, and OSA presenting with shortness of breath and desaturation with minimal exertion. PA = posteroanterior; LAT = lateral.*

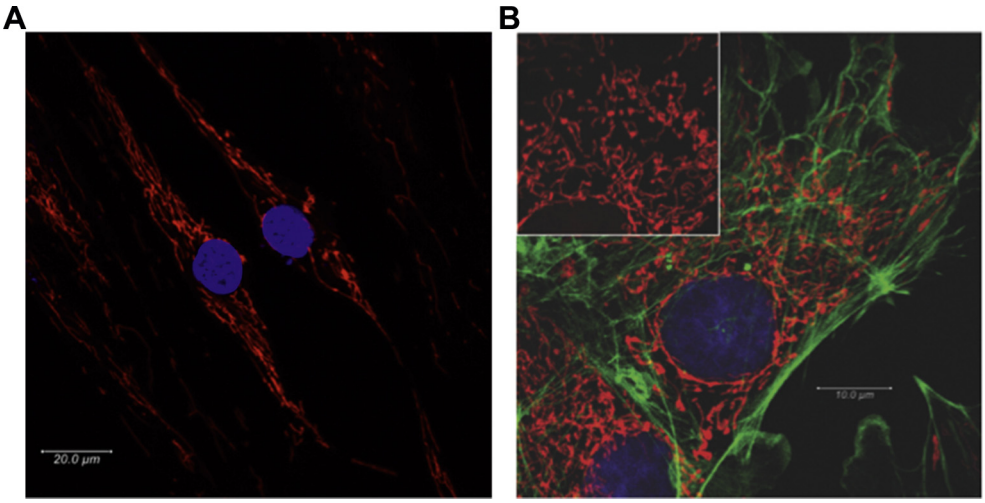


Figure 2 – *Pulmonary artery (PA) mitochondrial network. (A) Mitochondria in pulmonary artery smooth muscle cells from a normal patient were stained with 20 nM tetramethylrhodamine and imaged using confocal microscopy. Nuclei stained with NucBlue Live Cell Stain. (B) Bovine pulmonary artery (PA) endothelial cells stained for mitochondria (inset: red, MitoTracker Red CMXRos), phalloidin (green, Alexa Fluor 488), and nucleus (blue, 4′,6-diamidino-2-phenylindole) and imaged using confocal microscopy. All dyes/stains from Life Technologies (Carlsbad, CA).*

channels, causing an influx of Ca^{2+} into the cell down a 20,000:1 extracellular/intracellular Ca^{2+} gradient. This rise in cytosolic calcium and a subsequent rho kinase-mediated calcium sensitization causes PA constriction.[24,25]

Pharmacologic and electrophysiological experimentation using the patch clamp technique to study isolated PASMC from resistance PAs identified Kv as well as large conductance, voltage-gated calcium channels (Ca_L) in the effector mechanism of HPV.[25,26] 4-Aminopyridine is a Kv channel blocker and elicits pulmonary vasoconstriction in isolated perfused rodent lungs.[27] Additionally, Ca_L blockers nifedipine and verapamil inhibit the HPV response, whereas BAY K8644, a Ca^{2+}-channel agonist, enhances the vasoconstrictive response to hypoxia[24,28] (Fig 4). However, these effector components of HPV do not differ substantially between pulmonary and systemic arteries, both of which constrict in response to K^+ channel inhibitors and relax in response to calcium channel blockers[25]. Rather, the tissue heterogeneity in response to hypoxia results primarily from differences in oxygen sensor (mitochondrial) function between smooth muscle cells in pulmonary vs systemic arteries.

Molecular identification of the ion channels involved in HPV has revealed central roles for Kv1.5, a Shaker channel, and Kv2.1.[29,30] The Kv1.5 knockout mouse, for example, has markedly reduced HPV.[31] However, there is evidence for the involvement of other classes of K^+ and Ca^{2+} channels in the mechanism of HPV,[32] including two-pore K^+ channels,[33,34] which are active at very negative membrane potentials and thus are attractive targets for initiation of HPV. Although pharmacologic inhibition of these channels does not result in pulmonary vasoconstriction,[34] some likely contribute to the PASMC's electrophysiologic response to hypoxia. Likewise, in addition to the L-type Ca^{2+} channel, Ca^{2+} that contributes to HPV also derives from Ca^{2+}-induced Ca^{2+} release. HPV also reflects calcium sensitization.[35]

Although there is agreement that the mitochondria act as oxygen sensors and that ETC-derived ROS alter effector mechanisms that mediate vasoconstriction,[36-38] controversy remains regarding whether hypoxia elicits a rise or a fall in ROS/hydrogen peroxide levels.[32,39-43] Briefly, it has been proposed that hypoxia increases ROS and reflects autoxidation of the ETC due to distal inhibition of the ETC.[41,42] In contrast, our findings suggest that ROS production in PASMC increases as P_{O_2} rises and decreases as P_{O_2} falls. For example, we observe a rise in ROS levels in ductus arteriosus smooth muscle cells at birth as P_{O_2} increases.[44,45] Likewise, ROS levels are low in cardiac myocytes during ischemia and increase with reoxygenation during the reperfusion phase of myocardial ischemia/reperfusion injury.[46] We observe that ROS (including hydrogen peroxide) decrease in PASMC mitochondria during physiological hypoxia, reflecting a reduced rate of electron flux caused by reduced availability of the terminal electron acceptor (molecular oxygen).[23]

The basis for the discrepancies between those who find hypoxia to be an oxidized state with high ROS[41,42] vs those who find it to be a reduced state with low

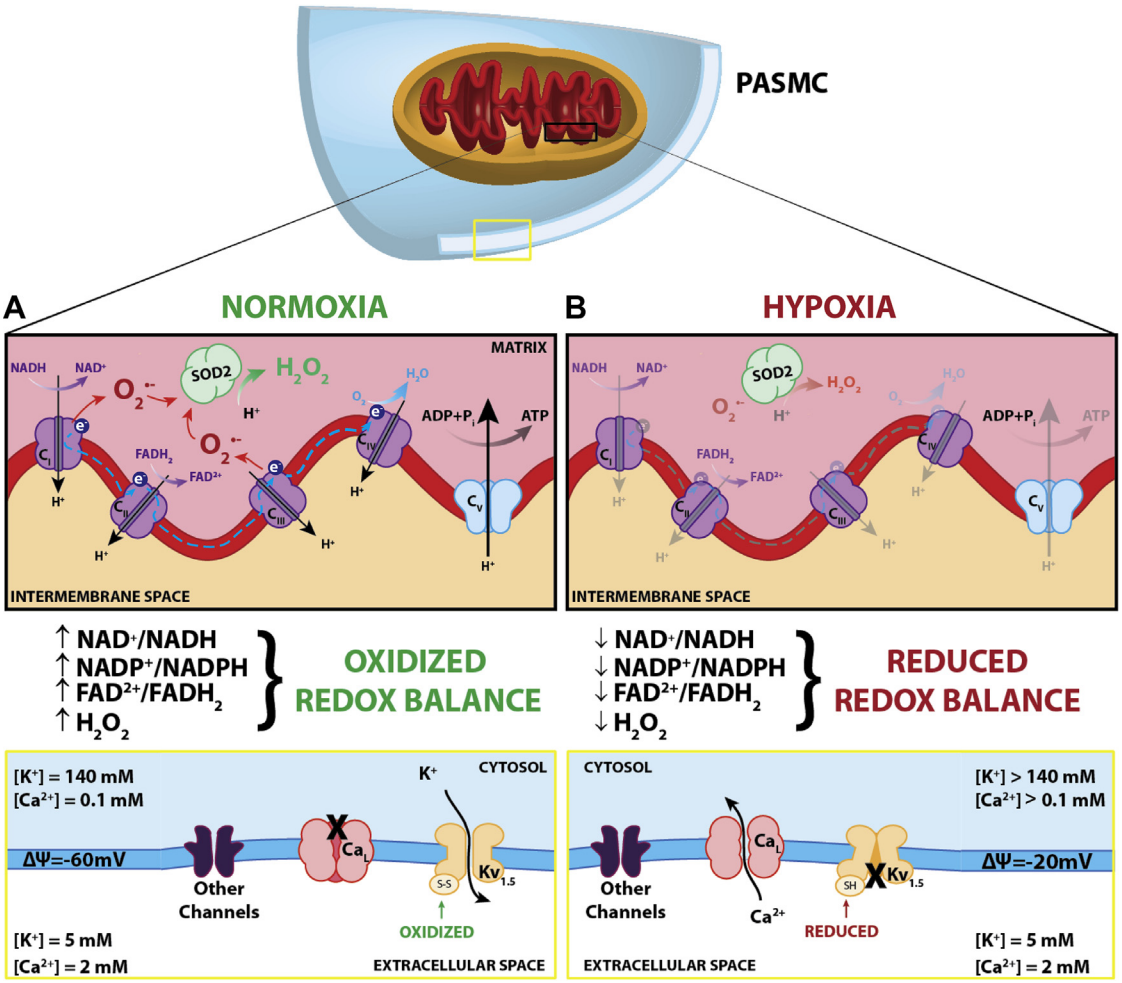
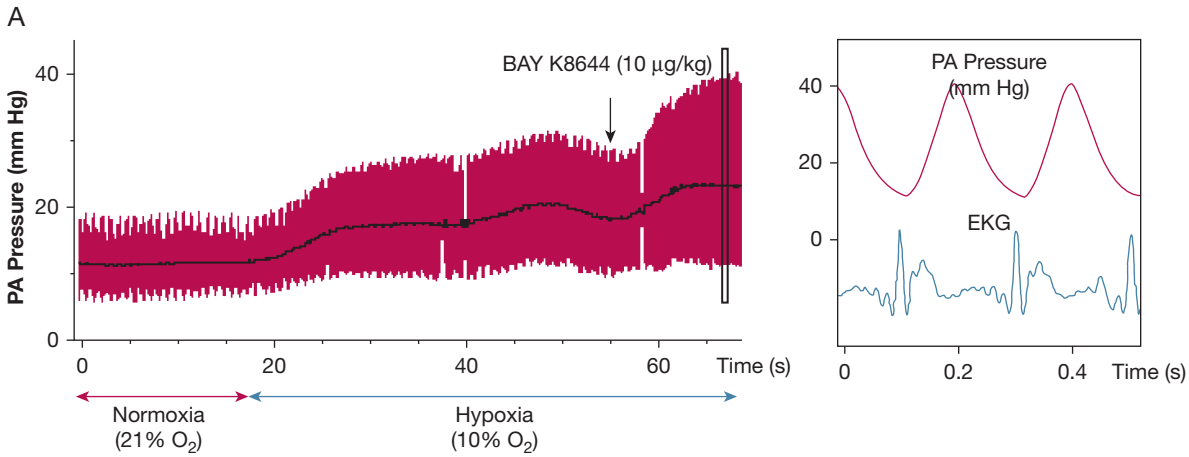


Figure 3 – *Mitochondrial redox oxygen sensing. The sensor-effector mechanism of hypoxic pulmonary vasoconstriction (HPV). (A) Under normoxic conditions, generation of reactive oxygen species (ROS) occurs at mitochondrial electron transport chain (ETC) complexes I and III, producing superoxide (O_2^-), which is converted to hydrogen peroxide (H_2O_2) by superoxide dismutase 2 (SOD2). Hydrogen peroxide, along with the oxidized redox couples (eg, nicotinamide adenine dinucleotide [NAD^+], nicotinamide adenine dinucleotide phosphate [$NADP^+$], and flavin adenine dinucleotide [FAD^{2+}]) maintain Kv1.5 sulfhydryl group oxidation and channel open state, resulting in tonic egress of K^+. This efflux of K^+ sustains the resting membrane potential ($\Delta\Psi$) of the cell at –60 mV and inhibits voltage-gated calcium channel [Ca_L]-mediated Ca^{2+} influx into the cell. (B) During hypoxia, the limited presence of oxygen (1) prevents generation of hydrogen peroxide, (2) decreases the ratio of oxidized/reduced redox couples, and (3) reduces sulfhydryl groups on Kv1.5 channels, causing them to close. The subsequent buildup of K^+ increases the resting membrane potential of the cell to –20 mV. This stimulates the opening of Ca_L, influx of Ca^{2+}, and subsequent activation of the contractile apparatus (ie, vasoconstriction). ADP = adenosine diphosphate; $FADH_2$ = flavin adenine dinucleotide; NADH = nicotinamide adenine dinucleotide.*

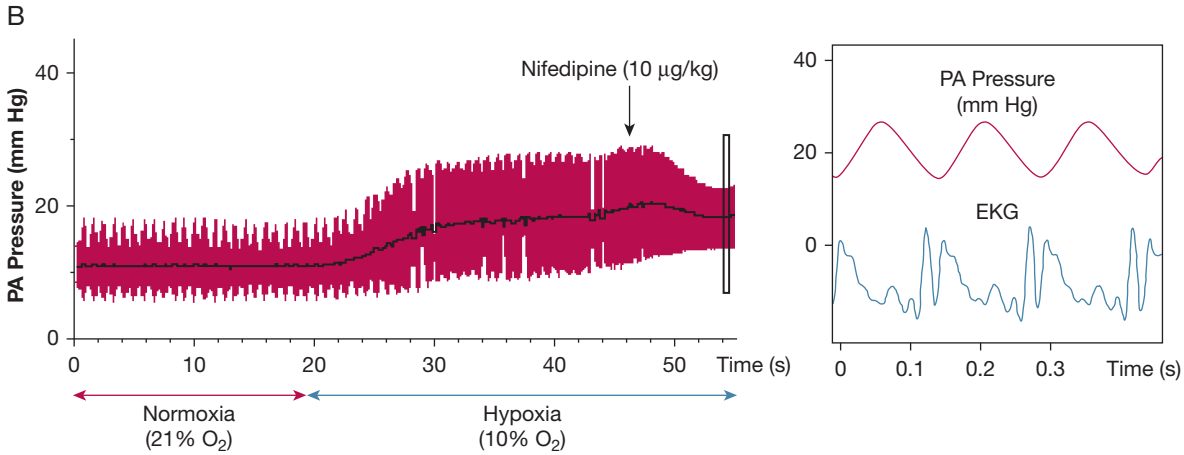
ROS[23,43] is unclear. Experimental discrepancies may relate to variation among groups in (1) the use of freshly isolated PASMC from resistance arteries, (2) the severity of hypoxia used, (3) attention to pH and P_{CO_2}, and (4) challenges in dynamic and accurate ROS measurement in subcellular compartments. Supporting the notion that hypoxia is a state of reduction (not oxidation), the opposing effects of hypoxia on the PA vs systemic vascular tone and cellular electrophysiology are mimicked by ETC inhibitors (eg, rotenone and antimycin A) and reducing agents (eg, dithiothreitol), rather than by ROS and oxidants.[9,47] Proposed mechanisms should be judged by the degree to which they explain core properties of HPV, which is rapid, reversible, evoked by mild hypoxia, and does not induce edema. Moreover, a unifying mechanism should account for the opposing effects of hypoxia on tone in the pulmonary circulation (constriction) vs the ductus arteriosus and systemic vasculature (vasodilatation).

Clinical Relevance of HPV

Although HPV is active in normal human physiology and patients with common lung diseases, it remains underappreciated by clinicians. In addition to optimizing $\dot{V}/\dot{Q}$ matching and systemic oxygen delivery, HPV is exploited surgically to enhance oxygenation.



Pressure (mm Hg)	Normoxia (21% O_2)	Hypoxia (10% O_2)	BAY K8644 (10 µg/kg)
sPAP	17	27	38
dPAP	7	10	12
mPAP	11	18	23



Pressure (mm Hg)	Normoxia (21% O_2)	Hypoxia (10% O_2)	Nifedipine (10 µg/kg)
sPAP	16	28	22
dPAP	7	10	13
mPAP	11	19	18

Figure 4 – *Voltage-gated calcium channels [Ca_L] and hypoxic pulmonary vasoconstriction (HPV). Ca_L agonist BAY K8644 and antagonist nifedipine exert opposing effects on HPV in the anesthetized hypoxic rat ventilated with 10% oxygen. This model of global hypoxia mimics changes that occur with ascent to altitude and results in a rapid increase in pulmonary artery pressure (PAP). (A) BAY K8644 enhances PA vasoconstriction during hypoxia. (B) Nifedipine administered during HPV inhibits Ca_L and reduces PAP. dPAP = diastolic PAP; ECG = electrocardiography; mPAP = mean PAP; sPAP = systolic PAP.*

HPV is critical to single-lung anesthesia for patients undergoing thoracic surgery such as lung tumor resections.[48] During these procedures, the patient is positioned on the side to facilitate surgical dissection, and single-lung ventilation is initiated using a double-lumen endobronchial tube (Fig 5A). During tube placement, the proximal and distal lumen tips are positioned above the carina and in the primary bronchus

of the target lung, respectively (Fig 5B). Cuffs around each lumen are inflated to prevent air leakage and allow for selective ventilation of the nonoperative lung and collapse of the operative lung (Fig 5C). HPV within the nonventilated lung reduces perfusion by minimizing shunting that would otherwise lead to intraoperative systemic hypoxemia (Fig 5D) and excessive bleeding in the operative field (Fig 5E).

The benefits of HPV during thoracic surgery may be attenuated by drugs or patient physiology. Volatile anesthetics, vasodilators, and hypothermia can inhibit HPV. Thus, anesthetic choices and temperature can be adjusted to optimize HPV in patients during single-lung ventilation. Historically, HPV has been enhanced pharmacologically using low doses of the respiratory stimulant almitrine. During single-lung ventilation, adding almitrine (4 μg/kg/min) to inhaled nitric oxide (NO) increases HPV and improves systemic oxygenation.[49] Although almitrine was withdrawn from clinical use because of its potential to cause peripheral neuropathy, this drug illustrates the value of enhancing HPV as a means of improving $\dot{V}/\dot{Q}$ matching and systemic oxygenation.

HPV also optimizes systemic P_{O_2} in patients with atelectasis, pneumonia, COPD, and asthma by reducing $\dot{V}/\dot{Q}$ mismatch and shunting (Table 1). During pneumonia or atelectasis, HPV optimizes systemic oxygen delivery by reducing perfusion of the hypoxic segment. HPV rapidly reverses on relief of atelectasis (eg, as occurs on removal of a mucous plug or with the use of incentive spirometry) or on resolution of pneumonia. The intensity of HPV varies between individuals and can diminish with disease or medication (Table 1).[50-64] For example, calcium channel blockers,

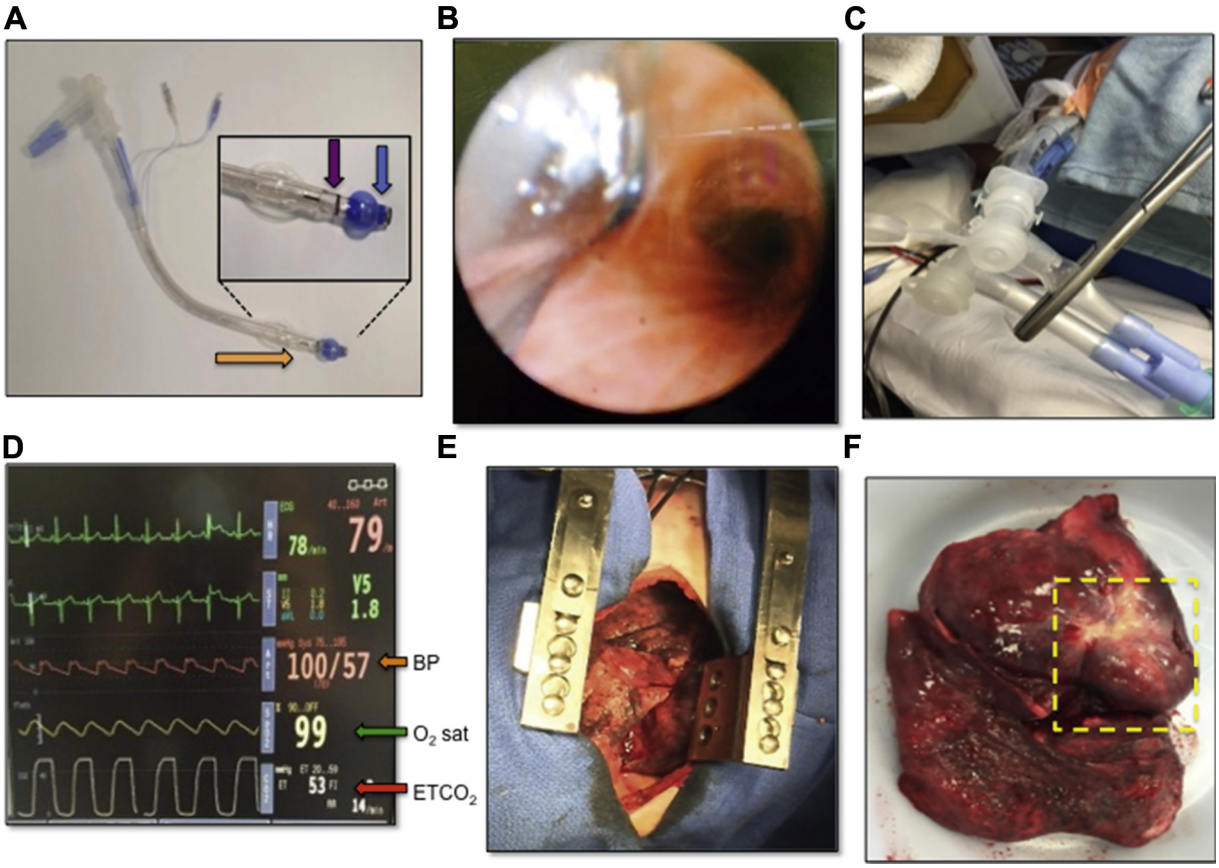


Figure 5 – *Clinical application of hypoxic pulmonary vasoconstriction (HPV). Maintenance of P_{O_2} during thoracic surgery through single-lung ventilation. (A) A Broncho-Cath double-lumen endotracheal tube (Covidien, Saint-Laurent, QC). The distal end (orange arrow) is inserted into the trachea until the bronchial lumen (inset, blue arrow) has entered either the right or left mainstem bronchus, whereas the tracheal lumen (inset, purple arrow) remains above the carina. (B) A bronchoscopic view of the carina from inside the tracheal lumen. The distal tip of the double-lumen endotracheal tube is seen entering the left mainstem bronchus to enable single-lung ventilation. (C) A clamp is placed on one limb of the ventilation circuit, allowing selective ventilation of the opposite lung. (D) Cardiorespiratory monitor during single-lung anesthesia/ventilation. The end tidal CO_2 is elevated to 53 mm Hg because of the decreased ventilation (red arrow), whereas oxygen (O_2) saturation is maintained at 99% (green arrow) and blood pressure (BP) remains stable (orange arrow) despite single-lung ventilation. (E) The nonventilated deflated lung undergoing surgery can be seen through an incision. Minimal bleeding is seen during surgery as a result of the HPV response. (F) Pneumonectomy specimen showing the complete lung removed with a large tumor (yellow box).*

TABLE 1] The Role of HPV in Respiratory Disease

Disease	Role of HPV	Treatment	References
HAPE	Exaggerated HPV; overperfusion of nonconstricted pulmonary vasculature	Calcium channel blocker nifedipine reduces the incidence of HAPE from 63% to 10%	50-53
Asthma	HPV maintains $\dot{V}/\dot{Q}$ balance during acute bronchoconstriction	IV isoprenaline decreases mPAP in an isolated perfused rat lung model of asthma (by 3-5 mm Hg)	53-56
COPD	HPV is reduced; however, the residual response improves $\dot{V}/\dot{Q}$ balance and systemic oxygenation	In COPD, almitrine (100 mg/d), a drug that enhances HPV, increases Pa_{O_2} from 52 to 59 mm Hg	53, 57-59
Pneumonia	Diversion of blood flow away from the diseased lobes of lung optimizes systemic P_{O_2}	Pneumonia impairs HPV in experimental models; in COPD with hypoxic exacerbations, IV prostaglandins increase systemic hypoxemia, consistent with the adverse effects of suppressing HPV	53, 57, 60-62
ALI/ARDS	HPV is reduced in ALI; however, the residual HPV improves $\dot{V}/\dot{Q}$ balance and reduces shunting	In an ovine model of ARDS, inhibition of inducible NOS restores HPV, increases Pa_{O_2}/Fi_{O_2}, and decreases shunt fraction	53, 57, 63, 64

ALI = acute lung injury; HAPE = high-altitude pulmonary edema; HPV = hypoxic pulmonary vasoconstriction; mPAP = mean pulmonary artery pressure; NOS = nitric oxide synthase; $\dot{V}/\dot{Q}$ = ventilation/perfusion.

which are commonly prescribed for systemic hypertension or coronary artery disease (comorbidities of COPD) can reduce HPV.[65] Illustrative of this point, patients with cor pulmonale (pulmonary hypertension secondary to COPD) given nifedipine (20 mg) exhibited a decrease in arterial P_{O_2} (from 52 to 47 mm Hg) and displayed a concomitant deterioration of $\dot{V}/\dot{Q}$ matching.[65] The route of administration determines the effects of PA vasodilators on HPV. Inhaled vasodilators (eg, inhaled NO) may enhance $\dot{V}/\dot{Q}$ matching, because they only reach well-ventilated lung segments (and thus do not impair HPV); conversely, IV vasodilators worsen $\dot{V}/\dot{Q}$ matching by relaxing arterioles serving poorly ventilated lung segments.[66] For example, after inducing PH in an isolated perfused rabbit lung model, Walmrath et al[66] demonstrated that although IV prostacyclin vasodilator treatment reduced mean pulmonary artery pressure (mPAP) (from 35 to 25 mm Hg), it also increased shunt fraction (to about 60%). In contrast, inhaled NO similarly decreased mPAP but maintained shunt fraction at about 25%.[66]

Suppression of HPV with Prolonged Exposure to Altitude

Suppression of HPV is a common adaptation to life at high altitude. The yak (*Bos grunniens*), native to the Himalayan region of Central Asia (altitudes > 3,500 m) has blunted HPV and thus maintains low PAP.[67] Conversely, domestic cattle (*Bos taurus*) are native to lowlands and exhibit substantial HPV at altitude, resulting in severe PH, edema, and right-sided heart failure in about 20% of cattle.[68] The sustained HPV and adverse pulmonary vascular remodeling causes right-sided heart failure, which leads to peripheral edema. Because of the cow's anatomy, this dependent edema collects in the neck (the brisket area), rather than in the legs, as would occur in humans. This neck swelling gave the name *brisket disease* to this lethal syndrome of excessive HPV and right-sided heart failure.[69] Cattle native to high altitudes are less prone to exaggerated HPV and brisket disease.[67,70] The crossbreeding of yak and cattle results in an animal that exhibits intermediate HPV. Anand et al[71] found that the dzo (a cross between a cow and a yak) had pulmonary hemodynamics similar to those of the yak. In contrast, crossbreeding a dzo to a bull results in a stol. Half of the stols had pulmonary hemodynamics similar to the yak, whereas the other half resembled the cow. This variation indicates a genetic basis for "altitude resistance" in these animals.[70,72] Newman et al[68] assessed the genetics of exaggerated HPV and high-altitude PH by comparing susceptible and resistant cattle (PAP at altitude, 86 ± 13 mm Hg vs 35 ± 1 mm Hg, respectively). In altitude-susceptible cattle, the expression of 46 genes was upregulated, whereas the expression of 14 genes was downregulated. Microarray analysis identified respiratory diseases and inflammatory disease pathways as being disordered in susceptible cattle. The susceptible phenotype was associated with abnormal interleukin-6, triggering

receptor expressed on myeloid cells, peroxisome proliferator-activated receptor, and nuclear factor κB signaling.[68] Whole-exome sequencing has implicated a mutation in the HIF-2α-encoding gene (endothelial PAS domain-containing protein 1 [EPAS1]) in the pathogenesis of high-altitude PH in cattle. A double variant in EPAS1 causing two nonsynonymous amino acid substitutions in the oxygen-dependent degradation domain of HIF-2α was found in 75% of cattle with elevated mPAP (> 50 mm Hg) and in all high-altitude cattle with PH (mPAP > 94 mm Hg) studied. It is hypothesized that this double variant is a gain of function mutation causing upregulation of multiple HIF-2α targets such as vascular endothelial growth factor and transforming growth factor-α.[73]

Human populations also display genetic variation in PAP at altitude. After millennia of living at altitudes > 4,000 m, native Tibetans exhibit minimal hypoxic PH (HPH) or polycythemia.[74] In contrast, HPH is prevalent in native Quechua Indians living in the Andean highlands of Ecuador and Bolivia at altitudes of approximately 3,500 to 4,000 m.[71,75] Similarly, children in Leadville, Colorado (the highest city in North America at about 3,100 m) commonly exhibit HPH. The severity of HPH in Leadville residents is similar to that of the Quechua, although the Coloradans live at much lower altitudes. Grover[70] showed that many healthy athletic children in Leadville exhibited HPH (mPAP, 28 mm Hg and 61 mm Hg at rest and during exercise, respectively). This indicates a high prevalence of moderate asymptomatic PH in a population of recent high-altitude residents.[50] It is thus hypothesized that the magnitude of HPV and HPH are inversely proportional to the duration of evolution at high altitude (25,000 years for Tibetans vs about 13,000 years for Andean Quechua[71] vs less than a century for populations in Colorado).[70] These studies in human and animal populations suggest genetic transmission of susceptibility or resistance to chronic hypoxia, and these variations likely relate to variations in the expression and function of components of the oxygen-sensing pathway.

Excessive HPV With Acute Exposure to Altitude Precipitates High Altitude Pulmonary Edema

Rapid ascent to high altitude without proper acclimation to the decreased oxygen tension can result in high-altitude pulmonary edema (HAPE), which is a noncardiogenic form of pulmonary edema that is characterized by cough, dyspnea, and reduced exercise performance, with usual onset within 2 to 5 days of ascension to altitudes > 2,500 m.[76] Exaggerated and heterogeneous HPV is implicated in the pathophysiology of HAPE[51,52] (Table 1). The rapid rise in PAP stresses and distends the arterial walls. Within a short time, these changes exceed the load capacity of the resistance PA resulting in rupture of the basement membrane and the alveolar-capillary barrier,[77] Interestingly, HAPE exhibits an individual susceptibility, being most common in people with exaggerated HPV. The 10% of whites that have exaggerated HPV are particularly susceptible to HAPE. Dehnert et al[78] assessed 421 healthy whites who were naive to high altitude; subjects were exposed to normobaric hypoxia (simulating the hypoxia found at 4,500 m), and PAP was measured using Doppler echocardiography. Thirty-nine subjects displayed exaggerated HPV during a simulated ascent to 4,559 m over 24 hours (systolic PAP in hypoxia, 51 ± 6 mm Hg). Four (13%) of these volunteers experienced HAPE during a 48-hour exposure. In contrast, no subjects with normal intensity of HPV (systolic PAP in hypoxia, 33 ± 5 mm Hg) experienced HAPE.[78] Moreover, in experimental models of ascent to altitude, suppression of HPV reduces HAPE. Isolated perfused rabbit lungs treated with acetazolamide (33 uM), which is an agent used clinically to prevent HAPE, exhibited less HPV (hypoxic mPAP about 15 mm Hg) than did control lungs (hypoxic mPAP about 20 mm Hg).[79]

In addition to rupture of the alveolar-capillary barrier, hypoxia also inhibits alveolar fluid clearance within the lung. Under normal conditions, reabsorption of sodium through sodium channels and exchangers generates an osmotic gradient within the lung, allowing the reabsorption of water. Hypoxia inhibits the activity of sodium exchangers, thereby decreasing sodium transport and ultimately reducing fluid reabsorption in the lung.[77]

HAPE is reversible provided that the patient receives adequate treatment in a timely manner. Improving oxygenation is the end goal, typically with supplemental oxygen and a rapid descent from altitude. Patients typically improve within hours of treatment with supplemental oxygen and rest. Complete clinical recovery is expected within days at low altitude.[80] In emergencies, when immediate descent is not feasible, treatment of HAPE with agents that inhibit HPV, such as nifedipine or sildenafil, can relieve symptoms until descent to a lower altitude can safely occur.[81]

Pseudohypoxia and Chuvash Disease

Another instance of pathologic HPV occurs in Chuvash disease. Named for the mid-Volga River region of Russia, patients with Chuvash disease have enhanced HPV, polycythemia, and PH, despite normal inspired oxygen concentrations.[82] Patients with Chuvash disease have a missense mutation within the von Hippel-Lindau gene (*VHL*). This mutation impairs the *VHL*'s ability to interact with the α-subunits of HIF-1α and HIF-2α. Under normoxic conditions, HIF proteins are hydroxylated by prolyl hydroxylases, which causes them to be ubiquitinated by *VHL*, thereby targeting HIF for proteasomal degradation. During hypoxia, HIF proteins are not hydroxylated nor are they bound by *VHL*, and thus degradation is impaired. The Chuvash *VHL* mutation impairs the ability of *VHL*-HIF interaction, resulting in normoxic HIF stabilization and paradoxical normoxic transcription of HIF-regulated genes, such as erythropoietin.[82-84] Thus, patients with Chuvash disease function as if they were exposed to chronic hypoxia due to derangement of normal oxygen sensing.

Fawn hooded rats, like patients with Chuvash disease, spontaneously develop PH and mild polycythemia with age. They too have normoxic activation of HIF-1α, although in fawn hooded rats this reflects epigenetic silencing of mitochondrial SOD2.[85] HIF is also a redox-regulated, oxygen-sensing mechanism[86]; however, its protean transcription-mediated effects have a slower onset than do the ion-channel-initiated vascular response to hypoxia. Conditions in which oxygen sensing is disordered remind us that pseudohypoxic signaling can contribute to human diseases such as HPH. Indeed, the Warburg paradigm in cancer is another example of impaired oxygen sensing leading to abnormalities of metabolism, cell proliferation, and apoptosis.[87]

Conclusions

The ability of PASMC in small resistance PAs to sense changes in oxygen and trigger HPV optimizes oxygen uptake and systemic oxygen delivery. HPV reflects an elegant interaction between a mitochondrial-redox sensor and an effector, which comprises redox-sensitive ion channels, enzymes, and transcription factors. HPV is important in the fetal circulation and is active in optimizing oxygenation in normal humans. HPV optimizes systemic oxygen delivery in various lung diseases, including atelectasis, pneumonia, and COPD. Clinicians should be mindful that inadvertent suppression of HPV by vasodilator drugs can lead to $\dot{V}/\dot{Q}$ mismatch and systemic hypoxemia; conversely, HPV can be inhibited to prevent or treat HAPE. HPV can also be exploited during single-lung ventilation to facilitate lung surgery.

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